REMARKS

The Office Action mailed 2 January 2002 has been received and carefully reviewed. Claims 2, 22, 29, 32, 48, 70, 71 and 74 having been cancelled, claims 1, 21, 23, 28, 30, 31, 33, 38-40, 45-47, 49-52, 54-56, 61-63, 72, 73 and 78 having been amended, and claims 82 and 83 having been added, the pending claims are claims 1, 3-13, 21, 23, 24, 28, 30, 31, 33-47, 49-69, 72, 73 and 75–83.

At page 2, the specification is amended to delete the phrase "largely because EphA2-specific antibodies previously have been difficult to generate." While reviewing the specification in connection with preparing this response, Applicants realized that this phrase may not accurately reflect the state of the background of the invention. Accordingly, to clarify how Applicants view the background of the invention, this phrase has been deleted.

The amendments to claims 1 and 47 reciting a "monoclonal antibody that specifically binds EphA2", and to claims 1, 28, and 45-47 reciting "antibody-EphA2 binding" are supported by the specification at, for example, page 4, lines 6-9.

The amendment to claim 21 and 23 reciting a "nucleic acid coding for the EphA2 protein" is supported by the specification at, for example, page 2, lines 29-30.

The amendment to claim 72, 73, and 78 reciting "intracellular location" of EphA2 is supported by the specification at, for example, at page 5, lines 21-24, in that the locations recited in the specification are intracellular locations.

Claims 28, 38-40, 47 and 61-63 are amended to delete the recitation of "potentially metastatic" cells. Claim 28 is further rewritten to depend from claim 1.

Claims 30, 31, 33, 40, 49-52 and 54-56 are amended to correct dependencies in view of the cancellation of the claims from which they depended.

Claims 71 and 78 are amended to delete the recitation of "change in expression level" of EphA2.

New claims 82 and 83 are supported by the claims as originally filed and by the specification at, for example, page 4, lines 6-9 and page 5, lines 8-32.

Rejection under 35 U.S.C. §112, First Paragraph

Claims 28-71 were rejected under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for a method of detecting the presence of metastatic cells, does not reasonably provide enablement for detecting potentially metastatic cells. Claims 29, 32, 48, 70 and 71 are canceled, rendering the rejection moot with respect to those claims.

This rejection is respectfully traversed. However, claims 28, 38-40, 47 and 61-63 are amended to delete recitation of "potentially metastatic" thereby obviating the rejection. Reconsideration and withdrawal of the rejection of claims 28-71 under 35 U.S.C. §112, first paragraph is, accordingly, requested.

The specification was objected to, and claims 4, 31, 50, and 54, were rejected under 35 U.S.C. §112, first paragraph, as failing to provide an adequate written description of the invention and failing to provide an enabling disclosure, because the specification does not provide evidence that the claimed biological materials are (1) known and readily available to the public; (2) reproducible from a written description (e.g., sequenced); or (3) deposited. The Examiner suggested deposit of cell lines producing the D7 and B2D6 antibodies along with a statement of availability.

This rejection is respectfully traversed. However, hybridomas D7 and B2D6 were deposited with the American Tissue Type Culture Collection on December 8, 2000, and the specification is amended herewith in view of the rejection to recite the indications of the biological deposit. A Statement of Availability is also submitted herewith. It is believed that the rejection is thereby obviated, and reconsideration and withdrawal of the rejection of claims 4, 31, 50 and 54 under 35 U.S.C. §112, first paragraph is, accordingly, requested.

Information Disclosure Statement

A Supplemental Information Disclosure Statement and 1449 form is submitted herewith, together with the documents listed thereon and four additional documents described in the Information Disclosure Statement but not listed on the 1449 form. Applicants request consideration of the documents listed on the 1449 form and also of the four documents (license agreements and material transfer agreements) described in the body of the Information Disclosure Statement, and return of the initialed form 1449 with the next Official Communication.

Supplemental Comments Concerning Withdrawn Rejection under 35 U.S.C. §103(a) and Request for Reconsideration

In the Office Action mailed July 5, 2001, claims 1-8, 10-13, 21-24 and 28-71 were rejected under 35 U.S.C. §103(a) as unpatentable over Pasquale et al. (U.S. Pat. No. 5,457,048) in view of Zantek et al., Mol. Bio. Cell, 9 (Supp): 134a, abstract 773 (1998) and Kinch et al., Hybridoma 17, 227-235 (1998), asserted in the Office Action July 5, 2001. That rejection was withdrawn in the Office Action mailed January 2, 2002.

The Examiner is requested to review the withdrawal of this rejection in view of the additional comments submitted herewith to insure that withdrawal of the rejection remains appropriate (or, in the alternative, to reassert the rejection if the Examiner deems it necessary). Applicants continue to believe that the rejection has been overcome and respectfully request confirmation of its withdrawal.

In their response to the rejection set forth in Office Action mailed July 5, 2001, Applicants argued that Kinch et al. is not an enabling disclosure of antibodies D7 and B2D6 because the hybridomas that make those antibodies were not publicly available. Applicants further indicated that the hybridomas were deposited with the ATCC on December 8, 2000. The Examiner is requested to note, in reviewing the withdrawal of the rejection as requested by

Applicants, that the first sale of D7 antibody occurred on or about October 15, 1998. Although D7 antibody was not publicly available at the time Kinch et al. was published, antibody D7 did become available sometime between about August 21, 1998, and about October 15, 1998. These dates are prior to the date of deposit with the ATCC. However, these dates are within the one year grace period preceding the filing date (August 17, 1999) of U.S. provisional application 60/149,259, to which priority in the instant application is claimed.

In addition, Applicants point out that Kinch et al. does not teach a "D7" antibody but instead teaches a "B2D7" antibody. Although the "B2D7" antibody taught in Kinch et al. may, indeed, be the "anti-Eck" "D7" antibody that became publicly available sometime after August 21, 1998, it is not reasonable to believe that one of skill in the art would understand they were one and the same. As noted in Applicants' previous response, there is no teaching in Kinch et al. that the "B2D7" antibody binds any specific tyrosine kinase, much less EphA2. Applicants therefore submit that one of skill in the art would have no reason to know that the D7 antibody that became publicly available sometime after August 21, 1998, was the same as the B2D7 antibody taught in Kinch et al.

For these reasons and for reasons stated in their previous response, Applicants continue to maintain that claims 1-8, 10-13, 21-24 and 28-71 are not rendered obvious by Pasquale et al. in view of Zantek et al.(1998) and Kinch et al. (1998).

Assignee Election, Revocation and Power of Attorney

Applicants filed an Election Under 37 C.F.R. §3.71, Revocation, Power of Attorney, and Certificate Under §3.73(b) on 31 October 2001. Confirmation of receipt of this communication (i.e., a date-stamped postcard) has not yet been received. It is believed that these papers may have been affected by a mail delay. A copy of the Election, Revocation and Power of Attorney as previously filed is attached hereto as Exhibit A for the convenience of the Examiner.

All future communications should be sent to the address given on the signature page of this Amendment and Response. The Examiner is asked to advise us the Applicant these papers were not received by the USPTO and need to be formally resubmitted.

Summary

It is respectfully submitted that the pending claims 1, 3-13, 21, 23, 24, 28, 30, 31, 33-47, 49-69, 72, 73 and 75–83 are in condition for allowance and notification to that effect is respectfully requested. The Examiner is invited to contact Applicants' Representatives, at the below-listed telephone number, if it is believed that prosecution of this application may be assisted thereby.

Respectfully submitted for
Purdue Research Foundation

By
Mueting, Raasch & Gebhardt, P.A.
P.O. Box 581415
Minneapolis, MN 55458-1415
Phone: (612) 305-1220
Facsimile: (612) 305-1228
Customer Number 26813

May 30, 2002
Date

By: _____
Victoria A. Sandberg
Reg. No. 41,287
Direct Dial (612)305-1226

CERTIFICATE UNDER 37 CFR §1.10:
"Express Mail" mailing label number: Ev073730822US Date of Deposit: 30 May 2002
The undersigned hereby certifies that this paper is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR §1.10 on the date indicated above and is addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

By: Jacquelyn K. Forborg
Name: JACQUELYN K. FORBORG

APPENDIX A - SPECIFICATION/CLAIM AMENDMENTS INCLUDING NOTATIONS TO INDICATE CHANGES MADE
Serial No.: 09/640,952
Docket No.: 290.0009 0101

Amendments to the following are indicated by underlining what has been added and bracketing what has been deleted.

In the Specification

The paragraph beginning at page 2, line 3, has been amended as follows:

Identification of increase expression of cell membrane tyrosine kinases would aid in the diagnosis and treatment of metastatic diseases. One such tyrosine kinase in EphA2. A member of the Eph family of tyrosine kinases known as Ephrins, EphA2 is a transmembrane receptor tyrosine kinase with a cell-bound ligand. Although cloned a decade ago, see Lindberg, R.A. and Hunter, T., "cDNA Cloning and Characterization of Eck, an Epithelial Cell Receptor Protein-tyrosine Kinase in the Eph/elk Family of Protein Kinases, "Mol, Cell. Biol. 10(12), 6316-6324 (1990), rather little is known about EphA2 function [largely because EphA2-specific antibodies previously have been difficult to generate].

The paragraph beginning at page 4, line 6, has been amended as follows:

Hybridomas which are specific to EphA2 have been selected. Use of the RIMMS strategy has resulted in the production of various monoclonal antibodies that specifically bind EphA2. Of the first four hybridomas chracterized, two recognize independent epitopes on EphA2. The first, D7, recognizes an intracellular eptope. The second, B2D6, binds to an extracellular epitope. D7 has proven to be highly specific for an intracellular epitope of EphA2 and this specificity provides much of the current basis for diagnosis of emtastatic tumors. Hybridoma D7, identified as "murine hybridoma D7," was deposited with the American Type Culture Collection (ATCC), 10801 University Blvd., Manassas, VA, 20110-2209, USA, on December 8, 2000, and assigned ATCC number PTA 2755. Hybridoma B2D6, identified as "murine hybridoma B2D6," was deposited with the American Type Culture Collection (ATCC), 10801 University Blvd., Manassas, VA, 20110-2209, USA, on December 8, 2000, and assigned ATCC number PTA 2754.

In the Claims

For convenience, all pending claims are shown below.

1. (Amended) A method for detecting the presence of metastatic cells in a cell population comprising the steps of

lysing at least a portion of the cell population,

incubating the lysed cells with a monoclonal antibody that specifically binds [reagent capable of specific binding to an epitope of] EphA2 to allow antibody binding to [said epitope] EphA2, and

detecting [compound-epitope] antibody-EphA2 binding.

3. The method of claim 2 wherein the epitope of EphA2 is an intracellular epitope of EphA2.

4. The method of claim 3 wherein the antibody is produced by hybridoma cell line D7.

5. The method of claim 2 wherein the antibody is labeled with a detectable label, and the detecting step includes detecting the label.

6. The method of claim 5 wherein the antibody is labeled with a fluorescent label and the detecting step comprises detecting the fluorescent label.

7. The method of claim 5 wherein the antibody is labeled with a radioactive label and the detecting step comprises detecting the radioactive label.

8. The method of claim 1 wherein the cell population comprises cells from a breast or prostate tissue biopsy.

9. The method of claim 1 wherein the cell population is harvested from a body fluid selected from the group consisting of blood, plasma, spinal fluid, saliva, and urine.

10. The method of claim 9 wherein the detecting step includes a diagnostic method selected from the group consisting of ELISA assays and flow cytometry.

11. The method of claim 1 wherein the incubating and detecting steps comprise western blotting methodology.

12. The method of claim 11 further comprising the steps of

providing a second antibody having phosphotyrosine specificity, and

western blotting with the second antibody.

13. The method of claim 1 wherein the metastatic cells are selected from the group consisting of breast, prostate, lung, and colon cancers.

21. (Amended) A method for detecting the presence of metastatic cells in a cell population comprising the steps of

incubating the cells with a reagent capable of specific binding to [a compound associated with EphA2 expression] a nucleic acid coding for the EphA2 protein, and

detecting reagent-compound binding.

23. (Amended) The method of claim 21 wherein the [compound] nucleic acid is [selected from the group consisting of EphA2, a fragment of EphA2,] DNA [coding for the EphA2 protein, and] or RNA [coding for the EphA2 protein].

24. The method of claim 21 further comprising the step of fixing the cells on a slide, and the detecting step comprises immunofluorescence staining.

28. (Amended) [A] The method [for detecting the presence of metastatic or potentially metastatic cells in a cell population comprising:

lysing at least a portion of the cell population;

incubating the lysed cells with a reagent capable of specific binding to EphA2 to allow binding of the reagent to EphA2; and

detecting reagent-EphA2 binding,] of claim 1 wherein [reagent] antibody-EphA2 binding is indicative of the presence of metastatic [or potentially metastatic] cells in the cell population.

30. (Amended) The method of claim [29] 1 wherein the antibody binds to an intracellular epitope of EphA2.

31. (Amended) The method of claim [29] 1 wherein the antibody is produced by hybridoma cell line D7.

33. (Amended) The method of claim [32] 5 wherein the antibody comprises at least one of a fluorescent label, a chemiluminescent label, a bioluminescent label, an enzymatic label, a chromogenic label and a radiolabel, wherein detecting reagent-EphA2 binding comprises detecting at least one detectable label.

34. The method of claim 28 wherein the cell population comprises cells selected from the group consisting of breast cells, kidney cells, prostate cells, lung cells and colon cells.

35. The method of claim 28 wherein the cell population comprises epithelial cells.

36. The method of claim 28 wherein the cell population comprises cells selected from the group consisting of breast cancer cells, kidney cancer cells, prostate cancer cells, lung cancer cells and colon cancer cells.

37. The method of claim 28 wherein the cell population comprises epithelial cancer cells.

38. (Amended) The method of claim 28 wherein the cell population comprises metastatic [or potentially metastatic] cancer cells.

39. (Amended) The method of claim 38 wherein the metastatic [or potentially metastatic] cancer cells comprise cells selected from the group consisting of breast cancer cells, kidney cancer cells, prostate cancer cells, lung cancer cells, and colon cancer cells.

40. (Amended) The method of claim 3 wherein the metastatic [or potentially metastatic] cancer cells comprise epithelial cancer cells.

41. The method of claim 28 wherein the cell population comprises cells from a tissue biopsy.

42. The method of claim 41 wherein the tissue comprises breast tissue or prostate tissue.

43. The method of claim 28 wherein the cell population comprises cells from a body fluid.

44. The method of claim 43 wherein the body fluid is selected from the group consisting of blood, plasma, spinal fluid, saliva, and urine.

45. (Amended) The method of claim 28 wherein detecting [reagent]antibody-EphA2 binding comprises utilizing a diagnostic method selected from the group consisting of an ELISA assay, a Western blot, and flow cytometry.

46. (Amended) The method of claim 28 wherein detecting [reagent] antibody-EphA2 binding comprises utilizing a Western blot; the method further comprising Western blotting with a second antibody having phosphotyrosine specificity.

47. (Amended) A method for detecting the presence of metastatic [or potentially metastatic] cells in a cell population comprising:

incubating at least a portion of the cell population with a monoclonal antibody that specifically binds EphA2 [reagent capable of binding to EphA2] to allow binding of the [reagent] antibody to EphA2; and

detecting [reagent] antibody-EphA2 binding, wherein [reagent] antibody-EphA2 binding is indicative of the presence of metastatic [or potentially metastatic] cells in the cell population.

49. (Amended) The method of claim [48] 47 wherein the antibody binds to an intracellular epitope of EphA2.

50. (Amended) The method of claim [48] 47 wherein the antibody is produced by hybridoma cell line D7.

51. (Amended) The method of claim [48] 47 wherein the antibody binds to an extracellular epitope of EphA2.

52. (Amended) The method of claim of claim [48] 47 wherein antibody-EphA2 binding yields a bound complex comprising a whole cell.

53. The method of claim 52 wherein detecting antibody-EphA2 binding comprises subjecting the bound complex to immunohistochemical staining.

54. (Amended) The method of claim [48] 47 wherein the antibody is produced by hybridoma cell line B2D6.

55. (Amended) The method of claim [48] 47 wherein the bound antibody comprises a detectable label; and wherein detecting antibody-EphA2 binding comprises detecting the label.

56. (Amended) The method of claim [48] 47 wherein the bound antibody comprises at least one of a fluorescent label, a chemiluminescent label, a bioluminescent label, an enzymatic label, a chromogenic label and a radiolabel; and wherein detecting antibody-EphA2 binding comprises detecting at least one detectable label.

57. The method of claim 47 wherein the cell population comprises cells selected from the group consisting of breast cells, kidney cells, prostate cells, lung cells and colon cells.

58. The method of claim 47 wherein the cell population comprises epithelial cells.

59. The method of claim 47 wherein the cell population comprises cells selected from the group consisting of breast cancer cells, kidney cancer cells, prostate cancer cells, lung cancer cells and colon cancer cells.

60. The method of claim 47 wherein the cell population comprises epithelial cancer cells.

61. (Amended) The method of claim 47 wherein the cell population comprises metastatic [or potentially metastatic] cancer cells.

62. (Amended) The method of claim 61 wherein the metastatic [or potentially metastatic] cells comprise cells selected from the group consisting of breast cancer cells, kidney cancer cells, prostate cancer cells, lung cancer cells, and colon cancer cells.

63. (Amended) The method of claim 47 wherein the metastatic [or potentially metastatic] cells comprise epithelial cancer cells.

64. The method of claim 47 wherein the cell population comprises cells from a tissue biopsy

65. The method of claim 64 wherein the tissue comprises breast tissue or prostate tissue.

66. The method of claim 47 wherein the cell population comprises cells from a body fluid.

67. The method of claim 66 wherein the body fluid is selected from the group consisting of blood, plasma, spinal fluid, saliva, and urine.

68. The method of claim 47 wherein detecting reagent-EphA2 binding comprises utilizing a diagnostic method selected from the group consisting of an ELISA assay, a Western blot, and flow cytometry.

69. The method of claim 47 wherein detecting reagent-EphA2 binding comprises utilizing a Western blot; the method further comprising Western blotting with a second antibody having phosphotyrosine specificity.

72. (Amended) A method for detecting the presence of cancer cells in a selected cell population comprising:

assaying at least a portion of the selected cell population for at least one of

[a change in EphA2 expression level;]

a change in EphA2 <u>intracellular</u> localization pattern; and

a change in EphA2 phosphorylation content

as compared to the [EphA2 expression level,] <u>intracellular</u> localization pattern and phosphorylation content in an analogous normal cell population;

wherein the change is indicative of the presence of a cancer cell in the selected cell population.

73. (Amended) The method of claim 72 wherein a change in [EphA2 expression level,] intracellular localization pattern or phosphorylation content is indicative of the presence of metastatic cancer cells in the cell population.

75. The method of claim 72 wherein assaying the cell population comprises incubating at least a portion of the selected cell population with a reagent capable of binding to EphA2 to allow binding of the reagent to EphA2; and detecting reagent-EphA2 binding.

76. The method of claim 75 wherein the reagent is an antibody.

77. The method of claim 76 wherein the antibody is produced by hybridoma D7 or B2D6.

78. (Amended) A method for determining the disease stage in a cell population comprising cancer cells, the method comprising:

assaying at least a portion of the cell population for at least one of

[EphA2 expression level;]

EphA2 intracellular localization; and

EphA2 phosphorylation content; and

determining the disease stage of the cancer cells.

79. The method of claim 78 wherein assaying the cell population comprises incubating at least a portion of the cancer cell population with a reagent capable of binding to EphA2 to allow binding of the reagent to EphA2; and detecting reagent-EphA2 binding.

80. The method of claim 79 wherein the reagent is an antibody.

81. The method of claim 80 wherein the antibody is produced by hybridoma D7 or B2D6.

82. (New) A method for detecting the presence of cancer cells in a selected cell population comprising:

assaying at least a portion of the selected cell population for at least one of

a change in EphA2 expression level;

a change in EphA2 intracellular localization pattern; and

a change in EphA2 phosphorylation content

as compared to the EphA2 expression level, intracellular localization pattern and phosphorylation content in an analogous normal cell population;

wherein the assaying the cell population comprises incubating at least a portion of the selected cell population with a monoclonal antibody, and wherein the change is indicative of the presence of a cancer cell in the selected cell population.

83. (New) The method of claim 82 wherein a change in EphA2 expression level is indicative of the presence of nonmetastatic cancer cells in the cell population.